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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP98/08155 (22) International Filing Date: 14 December 1998 (14.12.98) (30) Priority Data: 9726566.4 16 December 1997 (16.12.97) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BLACKLER, Paul, David, James [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). LEE, David, C. [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). SASSE, Michael, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: 5-[4-[2- (N-METHYL-N- (2-PYRIDYL)AMINO) ETHOXY]BENZYL] THIAZOLIDINE-2, 4-DIONE, MALEIC ACID SALT, HYDRATE AS PHARMACEUTICAL		
(57) Abstract A hydrate of 5-[4-[2- (N-methyl-N- (2-pyridyl)amino) ethoxy]benzyl] thiazolidine-2, 4-dione, maleic acid salt, characterised in that it: (i) comprises water in the range of from 0.4 to 2.5 %w/w; and (ii) provides an infra red spectrum containing peaks at 1749, 1703, 1645, 1623, 1365 and 736 cm ⁻¹ ; and/or (iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out in Figure II and/or (iv) provides a Raman spectrum containing peaks at 3106, 3069, 3002, 2961, 1750, 1718, 1684, 1385, 1335, 1229, 1078, 917, 428 and 349 cm ⁻¹ and/or (iv) provides a solid-state nuclear magnetic resonance spectrum containing chemical shifts substantially as set out in Table I; a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of such a compound or composition in medicine.		

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5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE,
MALEIC ACID SALT, HYDRATE AS PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the
5 pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO94/05659 discloses
certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic
activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

10 Compound (I) is disclosed solely as an anhydrous form. It has now been
discovered that Compound (I) exists in a novel form which is particularly suitable for
bulk preparation and handling. This can be prepared by an efficient, economic and
reproducible process particularly suited to large scale preparation.

The novel form also has useful pharmaceutical properties and in particular it is
15 indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus,
conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a novel form of 5-[4-[2-(N-
methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt
(the "Hydrate") characterised in that the Hydrate:

- 20 (i) comprises water in the range of from 0.4 to 2.5%w/w; and
(ii) provides an infra red spectrum containing peaks at 1749, 1703, 1645, 1623,
1365 and 736 cm^{-1} ; and/or
(iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out
in Table I and /or
25 (iv) provides a Raman spectrum containing peaks at 3106, 3069, 3002, 2961, 1750,
1718, 1684, 1385, 1335, 1229, 1078, 917, 428 and 349 cm^{-1} and/or
(iv) provides a solid-state nuclear magnetic resonance spectrum containing
chemical shifts substantially as set out in Table II.

Suitably the Hydrate contains water in the range of from 0.5 to 2%w/w, such
30 as from 1.5 to 2.0%w/w or from 1.85 to 2.0%w/w, for example 1.85, 1.86, 1.87 or
1.88%w/w.

In one favoured aspect, the Hydrate provides an infra red spectrum
substantially as set out in accordance with Figure I.

In one favoured aspect, the Hydrate provides an X-ray powder diffraction
35 (XRPD) pattern substantially in accordance with Figure II.

In a further favoured aspect, the Hydrate provides a Raman spectrum
substantially as set out in accordance with Figure III.

In yet a further favoured aspect, the Hydrate provides a solid-state nuclear
magnetic resonance spectrum substantially in accordance with Figure IV.

The present invention encompasses the Hydrate isolated in pure form or when admixed with other materials, for example the known anhydrous form of Compound I, the above mentioned reversibly rehydratable forms or any other material.

Thus in one aspect there is provided the Hydrate in isolated form.

5 In a further aspect there is provided the Hydrate in pure form.

In yet a further aspect there is provided the Hydrate in crystalline form.

The invention also provides a process for preparing the Hydrate, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt is crystallised from ethanol, suitably denatured ethanol, containing 15
10 to 25% by volume of water, for example 17.5% by volume.

Other aqueous solvents may also be used in the said crystallisation of the Hydrate, for example methanol, acetonitrile or ethyl acetate or mixtures thereof. The precise amount of water used in each of the alternative solvents will depend upon the particular solvent chosen, for example approximately 3% by volume in acetonitrile or
15 ethyl acetate. Methanol has also been shown to provide the hydrate when the crystallisation is conducted open to the atmosphere. Water can also be used as the crystallization solvent.

Compound I is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein
20 by reference.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

25 Conditions associated with diabetes include hyperglycaemia and insulin resistance, especially acquired insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as
30 anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with
35 the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly the Hydrate for use as an active therapeutic substance.

5 More particularly, the present invention provides the Hydrate for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Hydrate may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Hydrate and dosages thereof are generally as disclosed for Compound (I) in
10 International Patent Application, Publication Number WO94/05659.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Hydrate and a pharmaceutically acceptable carrier therefor.

The Hydrate is normally administered in unit dosage form.
15 The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

20 Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusible solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are
25 preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents.
30 The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include
35 sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to

distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Hydrate to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

5 In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Hydrate may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

10 In a further aspect the present invention provides the use of the Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

15 The following examples illustrate the invention but do not limit it in any way.

Example 1: Preparation of the Hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt.

5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione free base (6.0 g) and maleic acid salt (2.1 g, 1.05 molar equivalents) were heated in methanol (40 ml) to 55°C and held at this temperature for 30 minutes during which a solution was obtained. The solution was filtered, re-heated to 55°C, and then cooled to 0 - 5°C and stirred for two hours. The product was filtered, and dried at 52°C *in vacuo* for 18 hours to give the title compound (6.7 g, 84%). The water content of the product was 0.54%w/w.

10

The Hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt was also prepared by means of the following procedures:

Example 2

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (1.5 g, 4.2 mmole) and maleic acid (0.525 g @ 97.6% assay, 4.4 mmole, 1.05 mole equivalents) were heated in methanol (15 ml) and the temperature was held at 60°C. The resulting solution was filtered and then cooled to 0°C with magnetic stirring at which point a thick suspension was formed. The product, 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine -2,4-dione maleate, was isolated, washed with methanol and dried, *in vacuo*, at 52°C (Yield 1.4 g, 70.5%). Water content of the product was 2.0%.

Example 3:

5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione free base (6.0 g) and maleic acid (2.1 g, 1.05 molar equivalents) were heated in acetonitrile (60 ml) containing water (2ml) to 55°C and held at this temperature for 30 minutes during which time a solution was obtained. The solution was filtered, re-heated to 55°C, and then cooled to 0 - 5°C and stirred for two hours. The product was filtered, and dried at 52°C *in vacuo* for 18 hours to give the title compound (5.7 g, 72%). The water content of the product was 1.86 %w/w.

Example 4

The maleate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione anhydrate (3.0 g) was heated to 80°C in water (200 ml), then filtered hot and cooled to 20-25°C with magnetic stirring. The product was filtered, washed with denatured alcohol (20 ml) and dried at 50°C to give the title compound (1.6 g, 53%), water content 1.87%.

Example 5

The maleate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidione-2,4-dione anhydrate (2.0 g) was heated to 75°C in ethyl acetate (100 ml) containing water (3 ml), then filtered hot and cooled with magnetic stirring to 20-

25°C. The product was filtered and dried at 50 °C to give the title compound (1.43 g, 72%), water content 1.88%.

Example 6

- 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione free base (6.0 g) and maleic acid (2.1 g, 1.05 molar equivalents) were heated in denatured ethanol (60 ml) containing water (17.5% by volume) to 60°C and held at this temperature for 30 minutes during which a solution was obtained. The solution was filtered, re-heated to 55°C, and then cooled to 5 – 10°C and stirred for four hours.. The product was filtered, and dried at 52°C *in vacuo* for 18 hours to give the title compound (5.05 g, 62%), water content 1.85%.

CHARACTERISING DATA: The following characterising data was generated for the Hydrate from example 2:

15 A Infrared

- The infrared absorption spectrum of a mineral oil dispersion of the Novel form was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm⁻¹ resolution. Data were digitised at 1cm⁻¹ intervals. The spectrum obtained is shown in Figure I. Peak positions are: 3428, 3139, 3054, 1749, 1703, 1645, 1623, 1584, 1566, 1539, 1510, 1411, 1365, 1333, 1318, 1302, 1275, 1264, 1247, 1238, 1187, 1178, 1166, 1143, 1109, 1098, 1078, 1060, 1039, 1006, 979, 972, 956, 929, 924, 917, 896, 885, 864, 843, 810, 775, 764, 736, 718, 656, 604, 598, 587, 562 and 542 cm⁻¹

25 B X-Ray Powder Diffraction (XRPD)

- The XRPD pattern of the Novel form is shown below in Figure II and a summary of the XRPD angles and calculated lattice spacing characteristic of the Novel form is given in Table I.
- 30 A PW1710 X-ray powder diffractometer (Cu X-ray source) was used to generate the spectrum using the following acquisition conditions:

- | | |
|-----------------------|----------|
| Tube anode: | Cu |
| Generator tension: | 40 kV |
| 35 Generator current: | 30 mA |
| Start angle: | 3.5 °2θ |
| End angle: | 35.0 °2θ |
| Step size: | 0.02 |
| Time per step: | 4.550 s |

Table I.

X-Ray Powder Diffraction Angles and Calculated Lattice Spacing Characteristic of the Novel form.

5

Diffraction Angle ($^{\circ}2\theta$)	Lattice Spacing (Angstroms)
10.9	8.13
14.5	6.09
15.9	5.56
16.7	5.30
18.4	4.82
19.7	4.50
20.7	4.29
21.9	4.06
22.3	3.98
23.9	3.72
24.7	3.61
25.3	3.52
25.9	3.44
27.4	3.25
28.2	3.16
29.7	3.01
30.4	2.94
33.1	2.70

C Raman

10 A Raman spectrum of the Hydrate was recorded from a sample held in a glass vial using a Perkin-Elmer 2000R FT-Raman spectrometer at 4 cm^{-1} resolution and is shown in Figure III. Data were digitised at 1 cm^{-1} intervals. Excitation was achieved using a Nd:YAG laser (1064 nm) with a power output of 500mW. Peak positions are as follows: 3106, 3069, 3042, 3002, 2961, 2939, 2914, 2872, 1750, 1718, 1684, 1645, 1612, 1586, 1546, 1468, 1445, 1434, 1410, 1385, 1364, 1335, 1304, 1277, 1263, 15 1246, 1229, 1208, 1192, 1181, 1150, 1121, 1100, 1078, 1039, 1000, 980, 953, 917, 896, 883, 864, 843, 827, 805, 777, 742, 724, 657, 637, 607, 561, 540, 525, 497, 467, 452, 428, 400, 349, 317, and 297 cm^{-1} .

20

D NMR

The 90.55 MHz ^{13}C -CP-MAS NMR spectrum for the Hydrate is shown below in Figure IV. Chemical shifts are tabulated in Table II. Data were recorded at ambient temperature and 10kHz spinning frequency, with minimal prior grinding of the sample, using a Bruker AMX360WB spectrometer, with 1.6 ms cross-polarisation and a repetition time of 15s. Chemical shifts were referenced to the carboxylate signal of a glycine test sample at 176.4 ppm relative to tetramethylsilane and are judged accurate to within +/- 0.5 ppm. Peaks were not assigned.

Table II ^{13}C Chemical Shifts of the Hydrate

Chemical Shift (ppm)				
35.7	112.9 (2 resonances)	136.8	173.6	
37.9	119.7	143.0	176.6	
50.3	129.1	153.2		
57.0	133.2	157.4		
65.6	134.0	168.6		
109.3	136.1	171.7		

CLAIMS

1. A hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt.. characterised
5 in that it:
- (i) comprises water in the range of from 0.4 to 2.5%w/w; and
 - (ii) provides an infra red spectrum containing peaks at 1749, 1703, 1645, 1623, 1365 and 736 cm^{-1} ; and/or
 - (iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out
10 in Table I and /or
 - (iv) provides a Raman spectrum containing peaks at 3106, 3069, 3002, 2961, 1750, 1718, 1684, 1385, 1335, 1229, 1078, 917, 428 and 349 cm^{-1} and/or
 - (iv) provides a solid-state nuclear magnetic resonance spectrum containing chemical shifts substantially as set out in Table II.
- 15
2. A hydrate according to claim 1, wherein the water content is in the range of from 1.5 to 2.0% w/w.
3. A hydrate according to claim 1 or claim 2, which provides an infra red
20 spectrum substantially in accordance with Figure I.
4. A hydrate according to any one of claims 1 to 3, which provides an X-ray powder diffraction (XRPD) pattern substantially as set out in accordance with Figure II.
- 25
5. A hydrate according to any one of claims 1 to 4, which provides a Raman spectrum substantially as set out in Figure III.
6. A hydrate according to any one of claims 1 to 5, which provides a solid state
30 nuclear magnetic resonance spectrum substantially in accordance with Figure IV.
7. A hydrate according to any one of claims 1 to 6, in isolated form.
8. A hydrate according to any one of claims 1 to 7, in pure form.
- 35
9. A hydrate according to any one of claims 1 to 8, in crystalline form.
10. A compound in the form of a rehydratable form of a hydrate according to any one of claims 1 to 9.

11. A process for preparing a hydrate according to claim 1, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione. maleic acid salt is crystallised from ethanol containing 15 to 25% by volume of water.
- 5
- 12 A pharmaceutical composition comprising an effective, non-toxic amount of a hydrate according to claim 1 and a pharmaceutically acceptable carrier therefor.
13. A hydrate according to claim 1, for use as an active therapeutic substance.
- 10
14. A hydrate according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
- 15 15. The use of Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
- 20 16. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrate to a human or non-human mammal in need thereof.

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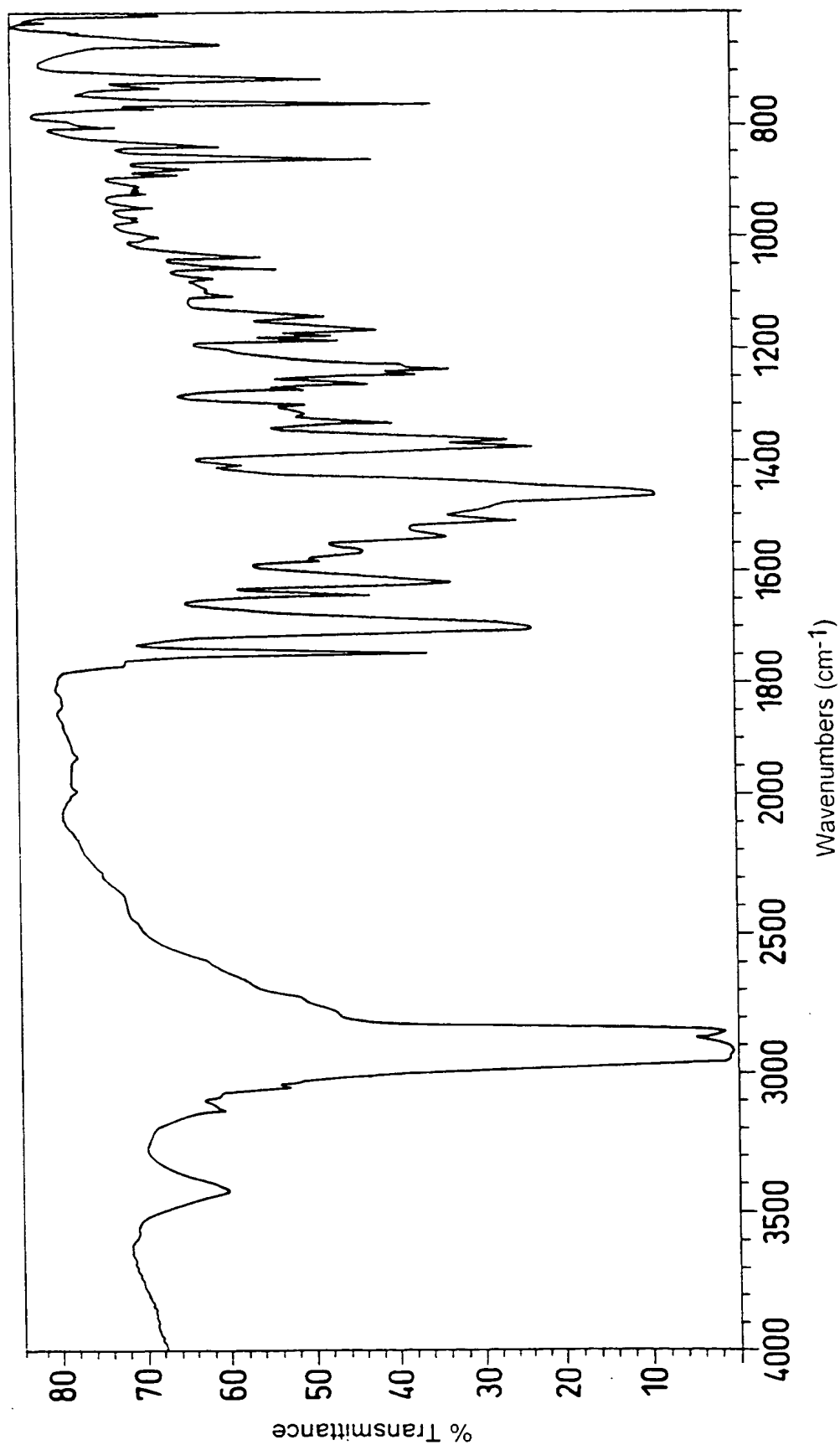


Fig. 1

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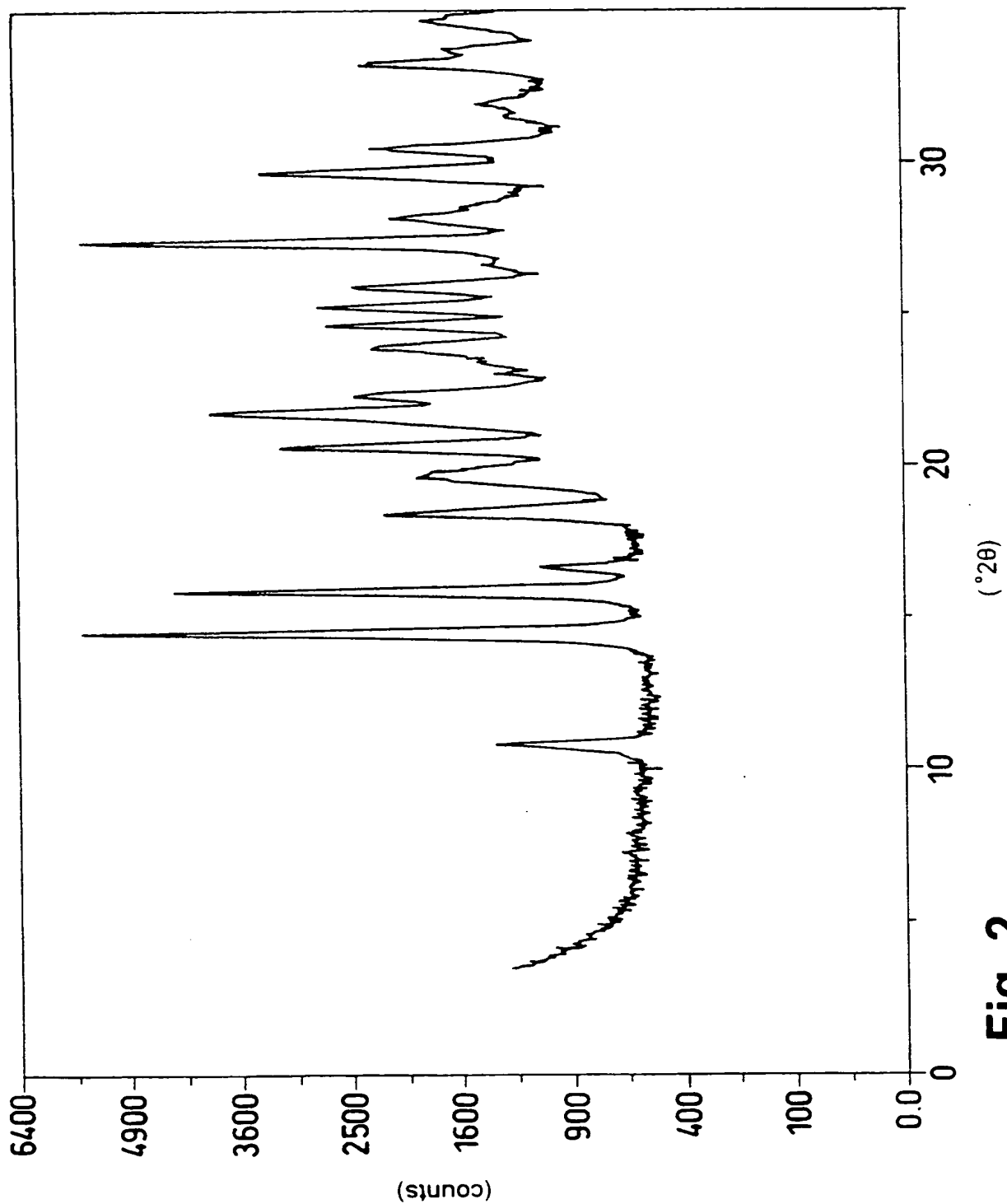
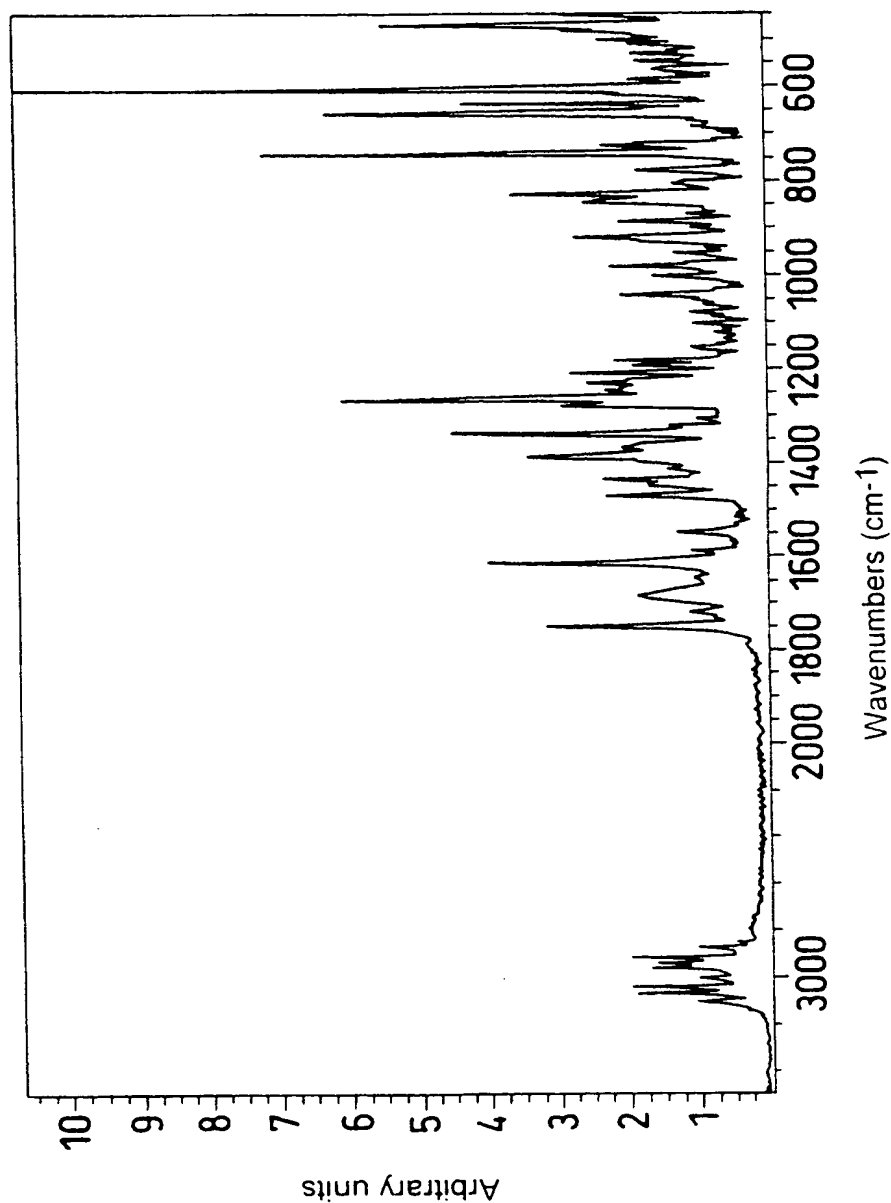


Fig. 2

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**Fig. 3** Raman Spectrum of Hydrate

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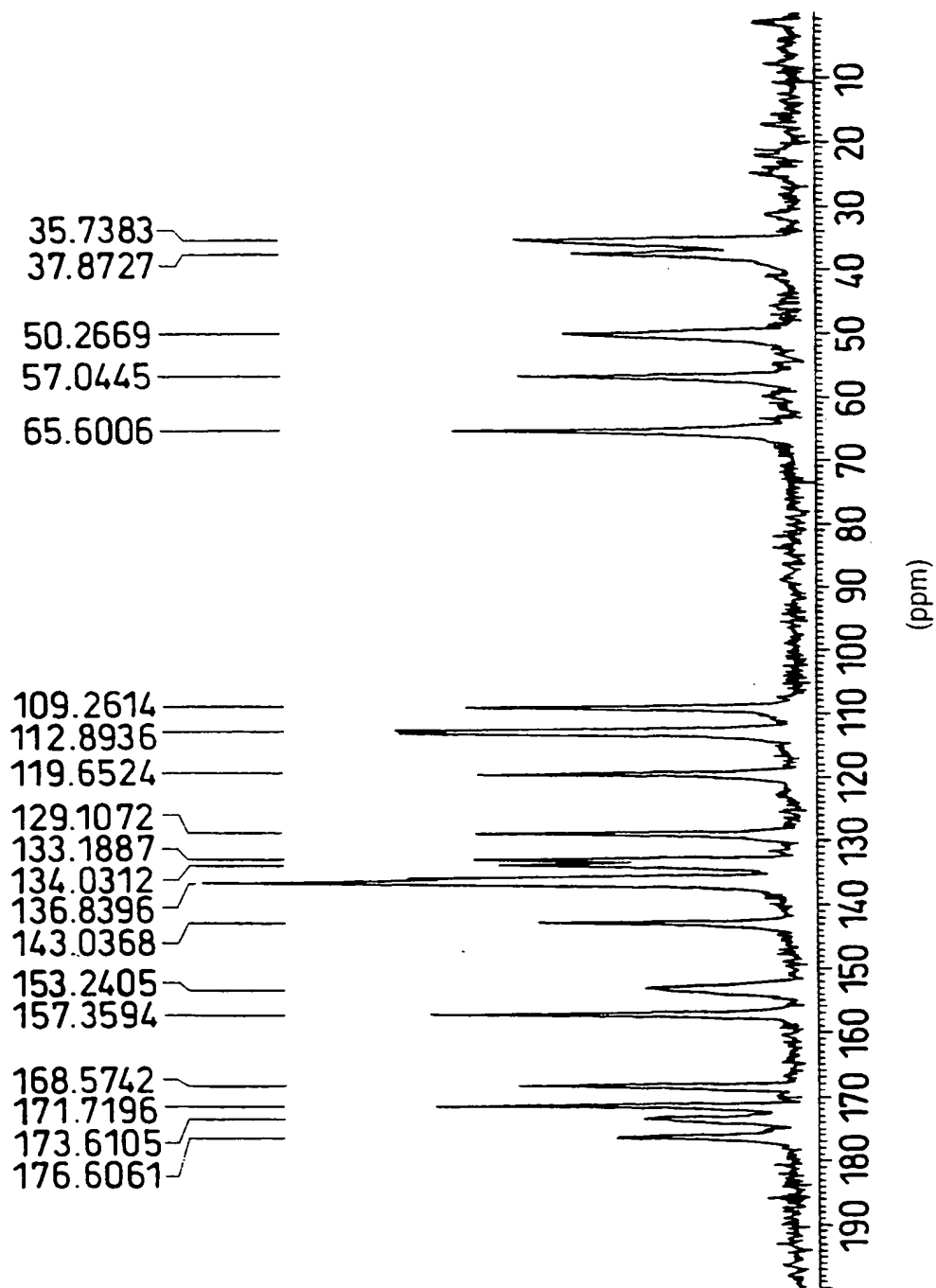


Fig. 4 ^1H Decoupled ^{13}C CP-MAS NMR spectrum of the Hydrate

INTERNATIONAL SEARCH REPORT

national Application No

PCT/EP 98/08155

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D417/12 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 cited in the application see page 5, line 13 - line 22; claims; examples 1,2</p> <p style="text-align: center;">--- -/--</p>	1-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 April 1999

Date of mailing of the international search report

23/04/1999

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INTERNATIONAL SEARCH REPORT

I. national Application No

PCT/EP 98/08155

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BARRIE C.C. CANTELLO ET AL: "Facile biocatalytic reduction of the carbon-carbon double bond of 5-benzylidenethiazolidine-2,4-diones.Synthesis of(+,-)-5-(4-(2-methyl(2-pyridylamino)ethoxylbenzyl)thiazolidine-2,4-dione(BRL49653),its (R)-(+)-enantiomer and analogues" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1.,1994, pages 3319-3322, XP002099539</p> <p>LETCWORTH GB</p> <p>see pages 3319,3321,first paragraph,compound 6 and page 3323,last example</p> <p style="text-align: center;">---</p>	1-16
A	<p>WO 95 21608 A (SMITHKLINE BEECHAM PLC ;BUCKINGHAM ROBIN EDWIN (GB))</p> <p>17 August 1995</p> <p>see page 4, line 28 - page 5, line 1; claims</p> <p style="text-align: center;">-----</p>	1,12-16

INTERNATIONAL SEARCH REPORT

international application No.

PCT/EP 98/08155

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/08155

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